References for Peer Review

The Office of Management and Budget (OMB) has published guidance for federal agencies regarding peer review
OMB Final Information Quality Bulletin for Peer Review, December 15, 2004
http://www.whitehouse.gov/omb/inforeg/peer2004/peer_bulletin.pdf

CDC/ATSDR Information Quality Peer Review
Procedures that CDC and ATSDR employ to conduct peer review of influential scientific information and highly influential scientific assessments that CDC disseminates to the public
http://www.cdc.gov/od/ophr/infoqualpeerreview.htm

ATSDR Peer Review Policy, revised March 1, 1996
http://www.atsdr.cdc.gov/science/prpolicy.html

The current guidelines provided to peer reviewers follows as attachment 1. Questions regarding peer review procedures should be directed to Jim Holler at 770-488-3358, jsh2@cdc.gov and Carolyn Tylenda at 770-488-3353, cbt9@cdc.gov.

DIVISION OF TOXICOLOGY AND ENVIRONMENTAL MEDICINE PEER REVIEW PROCEDURES

September, 2005

ATSDR is required by Section 104 of the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended by Section 110 (P.L. 99-499) of the Superfund Amendments and Reauthorization Act of 1986, to use peer reviewed literature in its publications. Within the Division of Toxicology, the Emergency Response and Scientific Assessment Branch (ERSAB) provides the coordination of the peer review of Toxicological Profiles, Technical Reports, and relevant unpublished studies. The development of these documents is coordinated by the Toxicology Information Branch. This peer review process is done in accordance with the legislation mentioned previously and within guidelines established within the ATSDR Peer Review Policy as revised March 1, 1996. The current contractor utilized for this peer review effort is Eastern Research Group, Inc. (ERG).

Information accepted as peer reviewed:

-Reports from peer reviewed journals,

-Federal government reports that have an agency publication number,

-Federal government contract reports that do not have an agency publication number but have a National Technical Information Service. (NTIS) number,

-Proceedings of a symposium, and

-Books.

Information not accepted as peer reviewed:

-A doctoral dissertation or thesis that has been prepared as a requirement for college graduation and has not subsequently published in a peer reviewed journal or a book,

-Non-peer reviewed journal (with exceptions e.g., Chemosphere, Environmental Health Perspective, and MMWR),

-Industry reports, and

-Federal government reports without an agency publication number or NTIS number.

Information we do not have peer reviewed:

-Material ,Safety Data Sheets (MDSD),

-Tables of numbers without supporting documentation to allow evaluation,

-Abstracts (Note: Only in rare instances are abstracts ever included in a profile.)

The process:

-ATSDR issues a task order to ERG for activity related to the contract. For most task orders, ATSDR submits: the list of profiled substances; set specific "Guidance for the Development of a Toxicological Profile;" and "Guidelines for Peer Review of ATSDR Profiles."

-ERG issues a work plan and cost estimate for performing the task order.

-ATSDR accepts the work plan and estimate, or asks for modifications and/or clarifications before approval.

-After approval of the task order for the profile set with the Profile Development Contractor, the schedule for profile set including peer review is shared with ERG.

-ERG provides ATSDR a list of potential reviewers (average of 5-8), in a prioritized order, with expertise in the field or the particular substance. In developing the list of potential reviewers ERG recognized that the panel should represent a balance of scientific perspectives relevant to the subject matter. ERG confirms with the potential reviewers that there are no real or perceived conflicts of interest, and informs them that current regulations require disclosure of the identity of peer reviewers, but not public attrition of specific comments to specific reviewers.

-The chemical manager (CM) reviews the list and then either approves the list or makes suggested changes in the prioritized order or suggested additions to the list.

-The CM decides which studies are to be peer reviewed. This may be done in consultation with the contract author. Using the criteria listed previously, the CM selects the studies to be peer reviewed. It is not necessary to peer review "all" unpublished studies, only the studies that may have a significant contribution (not "me too" data) to the data known about the substance. After the peer review of unpublished studies is approved by the Co-Project Officer, the list of unpublished studies to be reviewed is transmitted to ERG by E-Mail.

-ERG coordinates with the profile development contractor to prevent and handle any problems.

-ERG provides ATSDR and the profile contractor copies of the "Summary Report of Reviewer Comments on the Toxicological Profile for substance x" for each profile. This report may contain: The peer reviewers' summary reports; evaluation of unpublished studies; additional references and data submitted by the peer reviewers; and annotated pages from peer reviewers' profile documents.

-If applicable, the CM looks at each peer reviewer's evaluation of the unpublished study (this is in the "Summary Report of Reviewer Comments. ..") and decides if at least two of the three peer reviewers agree on the quality of the study. If the CM agrees, the CM has the contractor incorporate the study in the profile. If the study is not included, the profile guidance specifies what should be done.

-ERSAB will provide the CM a form to use in rating the reviewers.

Miscellaneous

-If an unpublished study is in a foreign language it must be translated before it is submitted for peer review.

If there are any questions regarding this procedures document or the peer review process, contact Jim Holler (770-488-3358) or Carolyn Tylenda (770-488-3355) from the Prevention, Response, and Medical Support Branch.

Attachment 1

GUIDELINES FOR PEER REVIEW OF ATSDR'S TOXICOLOGICAL PROFILES

The following guidelines are intended to provide structure for your review and to enable ATSDR to address your comments in a direct manner.

The toxicological profiles provide ATSDR's evaluations concerning whether adverse health effects occur and/or at what levels of exposure. Profiles are written with an emphasis on human health effects. They also contain information about health effects in animals, potential for human exposure, and environmental fate that may help the reader to determine the significance of levels found in the environment.

In these profiles, the emphasis is on providing succinct interpretations of the key literature. This distinguishes "profiles" from comprehensive criteria documents. The interpretations are expected to be useful to the informed public and health professionals who need a succinct interpretation of the toxicological data but may not have the resources to gather and consider all of the toxicological data themselves. Specifically, the profiles incorporate ATSDR's evaluations concerning the validity of particular studies and the inferences that can be made from them. The profile is not meant to contain all of the details necessary to support these interpretations. It is beyond the intended scope of the profile to present extensive details for users to weigh all the evidence themselves; such data are incompatible with the concept of a "profile." The authors have been instructed to avoid lengthy descriptions of studies. If there is uncertainty or controversy about a conclusion, however, a more detailed description of the studies that are the basis for the uncertainty may be included in the text. The description should be limited to those factors that are necessary to summarize the issue. Also, the "Supplemental Document" contains detailed descriptions of studies that provide no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs).

As you review the profile, if you wish to comment or suggest specific changes, please annotate directly in the text where the change or additional work is needed. After reviewing the document, prepare a summary report that addresses your major issues. Please present your comments in a constructive manner, be specific about the issues/changes suggested, and cite the section numbers whenever possible. f an issue has been missed or addressed improperly, please give specific information as to how it should be addressed. If you are citing a new reference, please provide a copy and indicate where in the text it should be included. Do not cite secondary sources except when the facts are widely accepted and non-controversial (as in the case of chemical identity information and physical property values).

Please note that there is a standard format for the profiles, including introductory standard language in some sections (in bold), and certain tables, figures, headings, etc. Comments

that relate to general format are welcome, and they will be considered in future revisions of the "Guidance for the Preparation of a Toxicological Profile."

This profile is intended to thoroughly cover potential exposures and potential health effects from
exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have essentially matured. Potential effects on offspring resulting from exposures of parental germ cells, or indirect effects on the fetus from maternal exposure during gestation should have been discussed as well. Relevant animal and *in vitro* models should also have been discussed.

Please answer the following questions in your review:

-Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be?

-Are there any general issues relevant to child health that have not been discussed in the profile and should be?

-If you answer yes to either of the above questions, please provide any relevant references.

CHAPTER 1. PUBLIC HEALTH STATEMENT

The intended audience for this chapter is the lay public, especially people living in the vicinity of a hazardous waste site or substance release. This chapter is written in active voice at an 8th to 10th grade reading level. To ensure that all relevant information has been incorporated, this chapter should be either reread after completing your review or, if only read once, read after reviewing the rest of the profile.

-The tone of the chapter should be factual rather than judgmental. Does the chapter present the important information in a non-technical style suitable for the average citizen? If not, suggest alternate wording.

-Major headings are stated as a question. In your opinion, do the answers to the questions adequately address the concerns of the lay public? Are these summary statements consistent, and are they supported by the technical discussion in the remainder of the text? Please note sections that are weak and suggest ways to improve them.

-Are scientific terms used that are too technical or that require additional explanation? Please note such terms and suggest alternate wording.

CHAPTER 2. RELEVANCE TO PUBLIC HEALTH

The purpose of this section is to evaluate and interpret the significance of existing toxicity data and, in some cases, speculate regarding the significance of this information as it relates to human health. Specifically, the text should address what effects are known to occur in humans; what effects have been observed in animals but not in humans; and what exposure conditions (route, duration, or level) are likely to be of concern to humans, especially around hazardous waste sites?

-Do you agree with those effects known to occur in humans as reported in the text? If not, provide a copy of additional references you would cite and indicate where (in the text) these references should be included.

-Are the effects only observed in animals likely to be of concern to humans? Why or why not? If you do not agree, please explain.

-Have exposure conditions been adequately described? If you do not agree, please explain.

CHAPTER 3. HEALTH EFFECTS

The intended audience for this chapter includes community-level public health officials, physicians, and concerned citizens. It is not intended to be a data review for toxicologists. Emphasis is placed on providing a summary evaluation of the weight of evidence, rather than on providing detailed descriptions of every relevant study. Scientifically prudent judgments and interpretations are both appropriate and desirable.

Section 3.1 INTRODUCTION

This introduction is standard language (in bold). A brief substance-specific discussion may be added to explain a complex topic.

Section 3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

This section begins with standard language (in bold). The purpose of this section is to specify the health effects that are associated with the substance and the degree of certainty attached to that association. Negative data also are presented. The text should contain conclusions about whether the effect occurs or not and about whether the studies are reliable. Human data should be presented before animal data. When

information suggests that an effect occurs, but the dose/response relationship is unclear, the issue should be discussed in the text.

In this section, toxicological effects are organized according to route of exposure (inhalation, oral, and dermal). Most of the information describing reliable studies is presented in the levels of significant exposure (LSE) tables. Text should be reserved for conclusions, discussions, explanations, etc. **NOTE**: Other routes of exposure (e.g., intraperitoneal, intramuscular, or subcutaneous) and in vitro studies are not discussed here; this information is included in Chapter 2: Relevance to Public Health.

ATSDR follows the National Research Council's "Guidelines for Assessing the Quality of Individual Studies," in Toxicity Testing: Strategies to Determine Needs and Priorities (NRC 1984).

Toxicity - Quality of Human Studies

-Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? If not, were the major limitations of the studies sufficiently described in the text without providing detailed discussions. If study limitations were not adequately addressed, please suggest appropriate changes.

-Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the profile? If not, did the text provide adequate justification for including the study (e.g., citing study limitations)? Please suggest appropriate changes.

-Were all appropriate NOAELs and/or LOAELs identified for each study? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

-Were the appropriate statistical tests used in the studies? Would other statistical tests have been more appropriate? Were statistical test results of study data evaluated properly? **NOTE**: As a rule, statistical values are not reported in the text, but proper statistical analyses contribute to the reliability of the data.

-Are you aware of other studies which may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included.

Toxicity - Quality of Animal Studies

-Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.

-Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

-Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the text? If not, did the text provide adequate justification for including the study (e.g., citing study limitations)?

-Were all appropriate NOAELs and LOAELs identified for each study? Were all appropriate toxicological effects identified for the studies? If not, please explain.

-If appropriate, is there a discussion of the toxicities of the various forms of the substance? If not, please give examples of toxicological effects that might be important for forms of the substance.

-Were the appropriate statistical tests used in the interpretation of the studies? If not, which statistical tests would have been more appropriate? Were statistical test results of study data evaluated properly? **NOTE**: As a rule, statistical values are not reported in the text, but proper statistical analyses contribute to the reliability of the data.

-Are you aware of other studies that may be important in evaluating the toxicity of the substance? If you are citing a new reference, please provide a copy and indicate where (in the text) it should be included.

Levels of Significant Exposure (LSE) Tables and Figures

These tables and figures are used to summarize health effects and graphically illustrate levels of exposure associated with those effects. These tables and figures present information on health effects by route, duration, increasing dose concentration, differences in response by species, minimal risk levels (MRLs) to humans for noncancer endpoints, cancer effect levels (CELs), and EPA's estimated range associated with an upper-bound cancer risk of 1 in 10,000 to 1 in 10,000,000.

All studies that are identified in the text **are not** presented in the LSE tables and figures. Studies that lack quantitative estimates of NOAELs and LOAELs, or that are not reliable, should not be selected for inclusion. All data in an LSE table must

be plotted on the corresponding LSE figure, with the exception that dermal data are presented in an LSE table without an accompanying LSE figure. For a description of MRLs and how to use the LSE tables and figures, see the "User's Guide" in the profile.

-Are the LSE tables and figures complete and self-explanatory? Does the "Users Guide" explain clearly how to use them? Are exposure levels (units, dose) accurately presented for the route of exposure? Please offer suggestions to improve the effectiveness of the LSE tables and figures and the "User's Guide."

-Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables?

-If MRLs have been derived, are the values justifiable? If no MRLs have been derived, do you agree that the data do not support such a derivation?

Evaluation of Text

-Have the major limitations of the studies been adequately and accurately discussed? How might discussions be changed to improve or more accurately reflect the proper interpretation of the studies?

-Has the effect, or key endpoint, been critically evaluated for its relevance in both humans and animals?

-Have "bottom-line" statements been made regarding the relevance of the endpoint for human health?

-Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provided and other data provided to you but not presented in the text.

-Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.

-Has the animal data been used to draw support for any known human effects? If so, critique the validity of the support.

Section 3.3 GENOTOXICITY

Section 3.4 TOXICOKINETICS

This section, like all preceding sections, should provide a synthesis and a weight-of-evidence analysis of toxicokinetics without detailed descriptions of individual studies (unless they are key to understanding the data). **[p. 48 of guidance states "with a**

description and discussion of key studies"] Special attention should be focused on significant toxicokinetic differences between high- vs. low-level exposure and sex or species differences (especially between humans and animals) that might be relevant in extrapolation of animal toxicity data to humans. As in the discussion of toxicological effects, the section should be organized by human vs. animal studies and, within these, by duration of exposure where possible.

-Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.

-Have the major organs, tissues, etc. in which the substance is stored been identified? If not, suggest ways to improve the text.

-Have all applicable metabolic parameters been presented? Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.

-Is there adequate discussion of the differences in toxicokinetics between humans and animals? What other observations should be made?

-Is there an adequate discussion of the relevance of animal toxicokinetic information for humans? If not, please explain.

-If applicable, is there a discussion of the toxicokinetics of different forms of the substance (e.g., inorganic vs. organic mercury)?

Section 3.5 MECHANISMS OF ACTION

The propose of this section is to provide a brief overview of known mechanisms of metabolism, absorption, distribution, and excretion, and then a discussion of any substance reactions or physiological processes that may affect these mechanisms. Have all possible mechanisms of action been discussed? If not, please explain.

Section 3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Section 3.7 CHILDREN'S SUSCEPTIBILITY

Section 3.8 BIOMARKERS OF EXPOSURE AND EFFECT

This section begins with standard language (in bold).

-Are the biomarkers of exposure specific for the substance or are they for a class of substances? If they are not specific, how would you change the text?

-Are there valid tests to measure the biomarker of exposure? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist.

-Are the biomarkers of effect specific for the substance or are they for a class of substances? If they are not specific, how would you change the text?

-Are there valid tests to measure the biomarker of effect? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist.

Section 3.9 INTERACTIONS WITH OTHER CHEMICALS

Discuss the influence of other substances on the toxicity of the substance.

-Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? If not, please clarify and add additional references.

-If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? If not, please clarify and provide any appropriate references.

Section 3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section begins with standard language (in bold) and identifies known or potential unusually-susceptible populations.

-Is there a discussion of populations at higher risk because of biological differences which make them more susceptible? Do you agree with the choices of populations? Why or why not? Are you aware of additional studies in this area?

Section 3.11 METHODS FOR REDUCING TOXIC EFFECTS

Where data or reasonable conjecture permit, this section describes directions of clinical practice and research that may help develop new methods for reducing toxic effects in individuals or populations exposed to a substance. It is intended to inform the public of existing clinical practice(s) and the status of research concerning such methods. It is not intended as a guide to treatment for poisoning.

When possible, a distinction should be made between differences in management and treatment following acute (generally high-level) vs. chronic (generally low-level) exposure. The section should not include dosages nor detailed descriptions of treatment regimens. The section should not read as though ATSDR is endorsing or recommending any particular treatment.

The first part of the section should be brief and provide a **very general** discussion regarding treatments that are known or expected to reduce peak absorption (lower initial blood levels) of the substance following exposure.

-Is the management and treatment specific for the substance, or is it general for a class of substances?

-Is there any controversy associated with the treatment? Is it a "well-accepted" treatment?

-Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?

The second part of the section should concentrate on methods to enhance the elimination of the absorbed dose or body burden, or remove a persisting metabolite or by-product of the substance from the body. It is appropriate to discuss treatments or research regarding interference with mechanisms of distribution or retention, or alteration of the pharmacokinetics of the substance so it has less chance of reaching the target organ(s).

-Are treatments available to prevent the specific substance from reaching the target organ(s), or are the actions general for a class of substances?

-Is there any controversy associated with the treatment?Is it a "well-accepted" treatment? If the discussion concerns an experimental method, do you agree with the conceptual approach of the method?

-Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?

-Are there treatments to prevent adverse effects as the substance is being eliminated from the major organs/tissues where it has been stored (e.g., as a substance is eliminated from adipose tissue, can we prevent adverse effects from occurring in the target organ[s])?

The last part of the section should focus on clinical or experimental methods that are known or expected to block the mechanism of toxic action at any point from initial interaction with body processes, to the actual physical damage or functional change.

-Are treatments available to prevent the specific substance from reaching the target organ(s), or are the treatment's actions general for a class of substances?

-Is there any controversy associated with the treatment? Is it a "well-accepted" treatment? If the discussion concerns an experimental method, do you agree with the conceptual approach of the method?

-Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?

Section 3.12 ADEQUACY OF THE DATABASE

This section begins with standard ATSDR language (in bold). "Data needs" are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized and a substance-specific research agenda will be proposed.

Existing Information on Health Effects of [Substance X]

Figure 2-X "Existing Information on Health Effects of [Substance X]" is provided to illustrate that positive and negative data exist. There is standard language (in bold) in the text. The dots in the figure do not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

-Do you know of other studies that may fill a data gap? f so, please provide the reference.

Identification of Data Needs

Carefully consider the data needs because they will serve as the basis for establishing a substance-specific research agenda. Data needs are discussed in Sections 6.8.1, 6.8.2 and 7.3.1 as well. The following questions also pertain to both of those sections.

-Are the data needs presented in a neutral, non-judgmental fashion? Please note where the text shows bias.

-Do you agree with the identified data needs? If not, please explain your response and support your conclusions with appropriate references.

-Does the text indicate whether any information on the data need exists?

-Does the text adequately justify why further development of the data need would be desirable; or, conversely, justify the "inappropriateness" of developing the data need at present? If not, how can this justification be improved.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

This chapter should contain very little text. Most of the information should be presented in tabular form.

> -Are you aware of any information or values that are wrong or missing in the chemical and physical properties tables? Please provide appropriate references for your additions or changes.

Is information provided on the various forms of the substance? If not, please explain.

CHAPTER 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

The level of detail in this chapter should be appropriate to an overview.

> -Are you aware of any information that is wrong or missing? If so, please provide copies of the references and indicate where (in the text) the references should be included.

CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE

This chapter includes general statements describing the ways in which substance releases are modified by time and environmental fate processes and the potential for human exposure to the substance via the different pathways.

> -Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.
>
> -Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.
>
> -Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the substance measured? Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.

-Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

-For Sections 6.8.1, Identification of Data Needs and 6.8.2, Ongoing Studies, answer the same questions presented in Section 3.12.2, Identification of Data Needs and 3.12.3, Ongoing Studies.

CHAPTER 7. ANALYTICAL METHODS

This chapter begins with standard language (in bold). Most information should be presented in tabular form.

-Are you aware of additional methods that can be added to the tables? If so, please provide copies of appropriate references.

-Have methods been included for measuring key metabolites mentioned previously in the text?

-If unique issues related to sampling for the substance exist, have they been adequately addressed in the text? What other discussion should be provided?

-For Section 7.3.1, Identification of Data Needs, answer the same questions presented in Section 3.12.2, Identification of Data Needs.

CHAPTER 8. REGULATIONS AND ADVISORIES

This chapter should present most information in tabular form. Information that is relevant but does not fit conveniently into the tabular format may be described in a brief paragraph. **NOTE:** In the table, only IARC and WHO recommendations are to be included under "International."

-Are you aware of other regulations or guidelines that may be appropriate for the table? If so, please provide a copy of the reference.

CHAPTER 9. REFERENCES

The intent of this section is to provide a reasonably complete list of references, whether cited in the text or not. Every reference cited in the text should appear with an asterisk in the bibliography.

-Are there additional references that provide new data or are there better studies than those already in the text? If so, please provide a copy of each additional reference.

UNPUBLISHED STUDIES (IF APPLICABLE TO REVIEW)

See previously stated criteria for evaluating the quality of human and animal studies.

-For each of the unpublished studies included with the profile, prepare a brief evaluation that includes your assessment of the:

-Adequacy of design, methodology, and reporting;

-Validity of results and author's conclusions; and

-Study inadequacies or confounding factors.

-Provide a summary of your conclusions? Do you agree or disagree with those of the author? If not please explain why.